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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,446	08/16/2000	Fang Fang	014357/0278749	9403

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/555,446	**Applicant(s)** FANG, FANG	
	Examiner Ulrike Winkler	**Art Unit** 1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 October 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *October 11, 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *7-10,19,20,27,29,31,33 and 37-42*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

The rejection of claims 7-9, 19, 20, 27, 29, 31, 33 and 37-42 under 35 U.S.C. §103(a) as being unpatentable over Adair et al. (WO 91/16927, see IDS October 20, 2003), Kipriyanov et al. (Protein Engineering, 1996), Pack et al. (Journal of Molecular Biology, 1995, see IDS February 12, 2001) and Hodits et al. (Journal of Biological Chemistry, 1995) **is maintained** for reasons of record.

The instant invention is drawn to a multivalent recombinant antibody, which include any multimeric configuration of two or more recombinant antibodies. The multivalent recombinant antibody is directed to ICAM-1. The antibody is formulated for the prevention of rhinovirus infection. The formulation includes antibodies to the LDL receptor. The claims are drawn to a method of administering the antibody for the prevention of the common cold or acute otitis.

Applicants' arguments and the examiners response are essentially the same of record see Office Action April 11, 2005. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this instance Adair et al. teach the use of a humanized anti-ICAM antibody for treating rhinoviral infections. The antibody of Adair et al. has the same affinity as the antibody of R6-5-D5, which according to applicants' response of November 22, 2004 (see page 8, is $7.7\ 10^{8}\ M^{-1}$ for ICAM-1). The antibody, like all other antibodies, comprises two binding sites. It was recognized by the Office that the Adair et al. reference alone (in isolation) would not meet the instant claim limitation, hence the rejection was made under the 35 U.S.C. §103(a). The

Kipriyanov et al. reference was cited because the reference teaches that increasing the valancey of a molecule increases the binding affinity of the molecule (see table 2, page 209). The association rate for the scFV:streptavidin tetramer was 35 times higher than the single chain scFV fragment alone and 8 times higher than the dimer (bivalent). Thus based on the teaching in Kipriyanov et al. the ordinary artisan would expect a tetravalent anti-ICAM molecule would have 8 times the binding affinity of a bivalent antibody, this would provide an anticipated binding affinity of $7.7\ 10^{8}\ M^{-1} * 8 = 7.7\ 10^{9}\ M^{-1}$ for a tetravalent compound.

Pack et al. teaches that a multivalent trimeric or tetrameric single chain antibody construct is obtained by the addition of the leucine zipper dimerization domain of GCN4 (a coiled coil domain). The GCN4 zipper is fused to the single chain antibody at the hinge region. Nature teaches that polymerizing low affinity molecules increases the functional affinity of the complex. This is observed in the decavalent IgM molecule.

Hodits et al. teaches the production of single chain fragment antibodies against the low density lipoprotein receptor (LDL). These antibodies were able to inhibit viral infection in cells (see figure 7). The antibody protection was increased by joining the single chain antibodies into a multivalent structure using a *myc*-sequence tag (see page 24084, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase the affinity of an antibody complex by increasing the valencey of the complex as taught by Kipriyanov et al. One having ordinary skill in the art would have been motivated to utilize the humanized recombinant antibodies taught by Adair et al. and to increase there binding capacity by fusing a polymerization sequence to the antibody. Formulating a combination of ICAM-1 directed antibodies and LDL antibodies into a single use formulation

would have been motivated by Hodits et al. which teaches that rhinoviruses gain entry into the host cell via the LDL receptor (minor group) and via the ICAM-1 (major group). A formulation containing antibodies directed to both groups would provide protection against rhinovirus displaying surface molecules associated different serotypes (see Hodits et al. page 24084, column 2, 2nd paragraph). Therefore, the instant invention directed to multivalent antibodies for the protection of rhinovirus infection is obvious over Adair et al., Kipriyanov et al. and Pack et al. in view of Hodits et al.

Conclusion

No claims allowed.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER

11/23/06